Received: 23 October 2017 | Accepted: 29 October 2017

DOI: 10.1002/edm2.7

ORIGINAL ARTICLE

WILEY Endocrinology, Diabetes & Metabolism Open Access

Twenty-four-hour growth hormone profiling in the assessment of acromegaly

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Summary

Objectives and background: Recent guidelines recommend insulin-like growth factor (IGF-1), random growth hormone (GH) and nadir GH on an oral glucose tolerance test (OGTT) for assessment of acromegaly. At this Regional Centre, the 24-hour GH profile has also been used.

Design, patients and measurements: We evaluated 57 GH profiles from 34 patients from 2008 to 2012. Samples were drawn every 2 hour and matched with 0800 GH, nadir GH after OGTT and IGF-1.

Results: Correlations between the mean 13-point profiles and mean 5-point profile, OGTT nadir and 0800 GH were as follows: r = .99, .99 and .90, respectively (P < .01 for all). The correlation between the mean 13-point profiles and IGF-1 was r = .32 P = .02. Of 5 patients with very high 0800 GH preoperatively (≥20 μg/L), mean 13-point GH reduced by 88%-99% postoperatively. IGF-1 did not normalize in these patients, and all required extra treatment. Preoperatively, all patients had concordant 0800 GH and IGF-1. Postoperatively, 6 patients had 0800 GH <1 μg/L and high IGF-1; only 2 of these had a 13-point mean >1 μg/L, but 5 required further treatment.

Conclusions: Growth hormone profiling is not necessary for assessing the majority of patients with acromegaly if there is confidence in the local IGF-1 assay. When undertaken, a 5-point profile is adequate. In patients with very high 0800 GH, 24-hour profiling was useful in demonstrating partial therapeutic success but did not alter management. Further work is needed to explore the possible role of GH profiling in stratifying patients with discordant IGF-1 and GH results.

KEYWORDS

acromegaly/metabolism, acromegaly/radiotherapy, acromegaly/surgery, biomarkers, glucose tolerance test, growth hormone, insulin-like growth factor 1

1 | INTRODUCTION

The Endocrine Society guidelines (2014) advocate the use of insulin-like growth factor (IGF-1), random growth hormone (GH) and nadir GH after oral glucose tolerance test (OGTT) for assessment of acromegaly.[1]

Insulin-like growth factor-1 is the most sensitive and specific test for the diagnosis of acromegaly. However, the IGF-1 recommendation in the guideline is predicated on the clinician having a knowledge of the specific assay used and its limitations including interassay variability.[2,3] It is also advised that the same assay be used in a given patient

over time. In clinical practice, preservation of the same assay has become increasingly difficult with laboratories undergoing more frequent tendering cycles.

In our regional centre, the IGF-1 assay available to us has changed over time and we have been unable to maintain multiple assays so as to keep the same assay true to a given patient. In these circumstances, the GH profile provided additional information albeit with a changing GH assay also over time.

Historically, we have used a 24-hour profile using 2-hourly GH measurements (13 results) rather than the usual 8-hour GH day profiles (5 results). These measurements began in a research setting over 30 years ago and became routine practice in our Regional Centre.

The relationship between serum GH and IGF-1 is linear below GH levels of 20 μg/L but above this level circulating IGF-1 levels plateau.[4-7] This effect has led to some concern that postoperative IGF-1 levels in large and metabolically active tumours may not adequately reflect partial therapeutic success. It has been postulated that GH profiling may provide additional information in these patients.

There is increasing recognition that in a minority of patients, GH and IGF-1 levels are discordant either in an intermittent or persistent way.[8] This may be exacerbated by surgery, external pituitary irradiation or medical treatment. The significance of recurrence, morbidity and mortality is unclear as are the best prognostic markers in this group. Multiple daytime GH measurements to establish either an area under the curve or a mean has been suggested by some authors for patients with either an elevated IGF-1 or normal OGTT or vice versa.[4,9-15]

We performed a retrospective analysis to examine the relationship between 24-hour GH profile results and IGF-1, random GH, nadir GH after OGTT and GH day profiles across treatment.

2 | MATERIALS AND METHODS

We evaluated 57 GH profiles from 34 patients, 25 of whom were new diagnoses, between April 2008 and December 2012 when both GH and IGF-1 assays remained unchanged. In 20 of these new diagnoses, profiles were available both preoperatively and 3 month postoperatively. Three of these patients also had an early postoperative 24-hour GH profile. Samples were drawn every 2 hour from 0800 to 0800 (13 time points) and matched with OGTT and IGF-1. GH was measured using Immulite 2000 solid-phase, 2-site chemiluminescent immunometric assay (CVs < 10%). IGF-1 was measured by immunoassay supplied by Immunodiagnostic Systems (Boldon, Tyne & Wear, UK) with CVs <7.5%. The 24-hour GH profile was also undertaken in patients during follow-up for various reasons such as persistently raised IGF-1 or discordant GH/IGF-1 results after initial treatment was completed or to assess the effect of additional treatment. Full profiling by OGTT, IGF-1 and 13-point GH was not available in all patients at all assessment points. Correlations were derived based on the available results.

Patient characteristics are set out in Table 1. All were enrolled in the national UK Acromegaly database with appropriate consents.

Failure to suppress GH secretion to <1 ng/mL following 75 g OGTT was considered diagnostic of acromegaly.

TABLE 1 Patient characteristics

Total	34
Gender	16 female
	18 male
Age at diagnosis (mean): Standard deviation	49.0 y
	14.2 y
Pituitary imaging at diagnosis	24 Macroadenoma
	9 Microadenoma
	1 unknown
Pre-operative somatostatin therapy	16
Surgery	29
Multiple surgery	1
Primary medical therapy	5
Postoperative external pituitary irradiation	11
Postoperative medical therapy	19

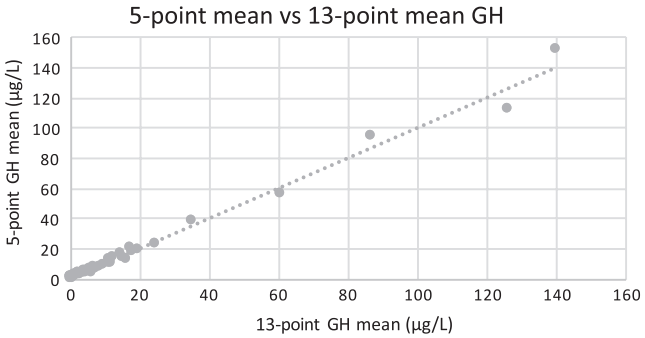

FIGURE 1 Thirteen-point mean growth hormone (GH) vs 5-point mean GH for whole cohort

3 | RESULTS

The correlation between the mean 13- and 5-point (0800-1600) profile was strong (r = .99, P < .01 Figure 1). Of the subgroup of 25 patients with pre- and/or postoperative evaluation, mean 13- and 5-point profiles were similar to the group as a whole (r = .99 and .98, respectively, P < .01). A similar relationship was seen between the 13-point profile and nadir GH on OGTT (r = .99 P < .01 Figure 2). Correlation between the mean 13-point profile and 0800 GH was strong (r = .90, P < .01 Figure 3). The correlation between mean 13-point profile and IGF-1 was moderate (r = .32, P < .05 Figure 4).

Preoperatively, there was full concordance between 0800 GH, IGF-1 and GH profiles, that is all were above their respective diagnostic thresholds/normal range.

The value of the 1400 sample during the 24-hour GH profile was also evaluated. Across the whole cohort, 50 of 57 profiles demonstrated concordant GH measures at 0800 and 1400. In 6 of the 7 discordant profiles, the 0800 sample was concordant with the IGF-1.

Of the 43 paired pre/postoperative results (20 patients, 3 of which had both immediate post-op and 3 month post-op results), 30 had both a high GH (≥1 μg/L) at 0800 and 1400 hour. Nine had both a

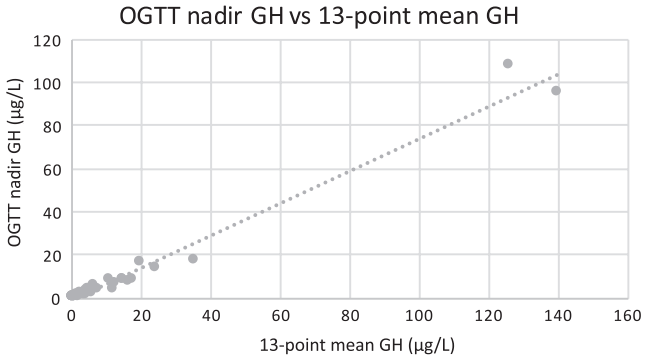

FIGURE 2 Thirteen-point mean growth hormone (GH) vs nadir GH on oral glucose tolerance test (OGTT)

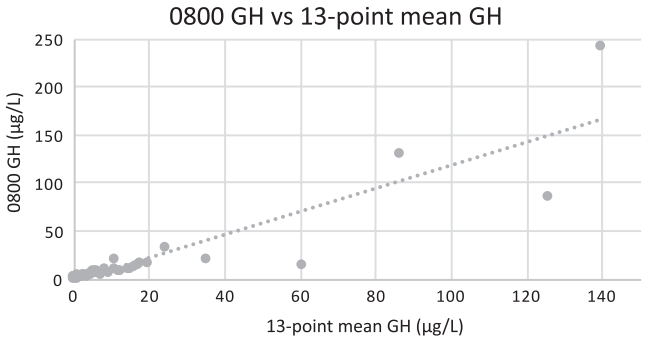

FIGURE 3 Thirteen-point mean growth hormone (GH) vs 8am GH

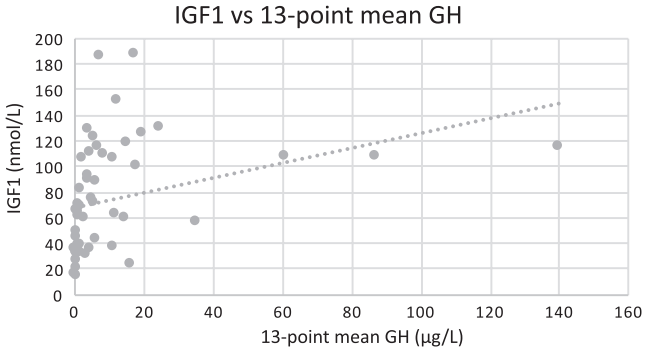

FIGURE 4 Thirteen-point mean growth hormone (GH) vs IGF-1

low GH (<1 μg/L) at 0800 and 1400 hour. There was discordance in 4 patients. Of these, 2 had a high 0800 GH, low 1400 GH with high IGF-1. One had low 0800 GH, high 1400 GH with high IGF-1 and one had low 0800 GH, high 1400 GH with normal IGF-1. Overall, therefore, the 0800 GH was concordant with the IGF-1 in 3 of the 4 patients.

Six patients had discordant results postoperatively with normal 0800 GH but elevated IGF-1. Their biochemical profiles are illustrated in Table 2. Of these 6 patients, clinical remission ensued in one patient, Patient 2. This was reflected by normalization of the IGF-1 by 19 months postoperatively, and this was predicted by normal OGTT, 5-point and 13-point profiles. The 13-point GH profile in Patient 4 demonstrated a mean GH >1 μg/L where the 5-point GH profile mean was <1 μg/L. However, IGF1-1 did not settle at 6 months, pituitary imaging demonstrated significant residual tissue and symptoms persisted. Unfortunately, an OGTT was not available in this patient and this may have predicted persistent disease without the need for a 24-hour profile. The night means mirrored the 13-point means in all 6 postoperative discordant patients and mirrored the 5-point mean in 5 of the 6 patients.

In the 5 patients with very high 0800 GH (≥20 μg/L) preoperatively, reductions in GH postoperatively were considerable (88%-99%) and in 1 patient mean GH was <1 μg/L. In all 5 patients, IGF-1 was not normalized being modestly reduced (34%-64%) and in 1 patient elevated by 33%. Persistent disease was deemed to be present in all 5 patients in this group. A 13-point profile did not add to the clinical management of these patients. Their profiles are summarized in Table 3.

We found that in the 16 patients with very high IGF-1 levels preoperatively (>100 nmol/L), it took longer than 3 months to plateau postoperatively. In 11 of these, repeat sampling 6-12 months later showed further reduction without extra treatment.

Table 4 illustrates the stratified predictive value of 0800 GH postoperatively on OGTT nadir GH, 5-point and 13-point GH means among the subgroup of postoperative patients where each measure was available for comparison. An 0800 GH of <2.5 μg/L was highly predictive of nadir GH within the same range on OGTT and of mean GH in the same range on both 5 and 13 point day curves. Similarly, an 0800 GH of >5.0 μg/L was predictive of nadir GH on OGTT and day curve means within the same range. For those patients with an 0800 GH between these 2 ranges (ie, 2.5-5.0 μg/L), the predictive value was much less and as such the 0800 GH was not predictive of GH status as measured by OGTT, 5-point or 13-point profiles.

4 | DISCUSSION

The 13-point GH profile as an extension of the 5-point profile was adopted in a research setting in our Centre in the 1990s.[15-19] We are unaware of any other groups using the 13-point 24-hour GH profile in clinical practice. Publications using this assessment initially explored the dose response of octreotide in resistant acromegaly. With the development of long-acting analogues, the 13-point GH mean was also used to demonstrate its comparable efficacy to subcutaneous octreotide.[17] The latter study demonstrated a significant correlation between mean 24-hour GH levels and serum IGF-1 (r = .39, P = .03), similar to the current study (r = .32, P < .02), although the assays used previously were different (serum GH double-monoclonal antibody technique) (Delfia) and serum IGF-1 was measured by RIA (Nichols CA).

The literature on 24-hour GH profiling in acromegaly is sparse. When profiling has been undertaken in research settings, this has typically been labour-intensive with GH measurements being drawn every 10-20 minutes.[4,21] The recent study by Roelfsema et al[22] demonstrated that in patients with active acromegaly and those on SSA therapy, a shorter day curve correlated strongly with a 144-point 24-hour GH profile.[22]

TABLE 2 Discordant postoperative patients: normal 0800 GH (growth hormone) with high IGF-1 (insulin-like growth factor-1)

	08:00 GH (μg/L)	IGF-1 (nmol/L)	IGF-1 Norm range	OGTT nadir GH (μg/L)	5-point profile mean GH (μg/L)	13-point profile mean GH (μg/L)	1400 GH (μg/L)	Night mean GH 1800-0600 h (μg/L)	Postoperative MRI imaging	Outcome
1	0.2	44.3	7.0-30.0	0.2	0.50	0.39	1.0	0.31	Large residual tissue volume, little change vs pre-operative imaging	Persistent disease requiring medical therapy. IGF-1 began to rise after 24 mo with recurrence of symptoms.
2	0.1	65.3	15.0-45.0	<0.1	0.16	0.60	0.2	0.99	Very good clearance. Thin rim of tissue in the base of pituitary fossa.	Clinical remission. IGF-1 ultimately normalized by 19 mo.
3	0.1	38.2	7.0-30.0	0.3	0.48	0.76	0.4	0.57	Residual tissue, 11 × 7 × 8 mm	Persistent disease requiring radiotherapy and medical therapy. IGF-1 failed to normalize, rise in GH on oral glucose tolerance test (OGTT) at 12 mo.
4	0.5	61.2	7.0-30.0	n/a	0.48	1.25	0.2	1.93	Significant quantity of residual tissue remains, 18 × 14 × 8 mm	Persistent disease requiring medical therapy. IGF-1 began to rise after 12 mo with recurrence of symptoms.
5	0.8	36.5	7.0-30.0	n/a	1.20	1.35	0.9	1.53	Small quantity of residual tissue.	Persistent disease requiring medical therapy. IGF-1 rise and random GH rise after 16 mo.
6	0.9	32.9	7.0-30.0	n/a	0.78	0.77	0.8	0.76	Residual tissue	Persistent disease requiring radiotherapy and medical therapy both prior to this profiling undertaken at 12 y postoperatively. IGF-1 remains stable just above the reference range without symptoms.

TABLE 3 High pre-operative 0800 GH (growth hormone) cohort

Patient	Pre-op 0800 GH	3 mo post-op 0800 GH	GH change post-op (%)	Pre-op 13-point GH mean ± SD	3 mo post-op 13-point GH mean ± SD	Pre-op IGF-1	3 mo post-op IGF-1	6 mo post-op IGF-1	IGF-1 normal range	3 mo post-op MRI pituitary	Further treatment
1	32.4	0.2	−99	24.55 (4.5)	0.39 (0.3)	130	44.3	42.9	15-35	"Slight reduction in tumour bulk but minimal change vs pre-operative images"	Somatostatin analogue and dopamine agonist
7	129	6.3	−95	86.70 (24.3)	5.44 (3.0)	108	71.6	66.7	15-45	"Small nodule of residual tumour"	Somatostatin analogue
8	84.8	9.4	−89	126.08 (44.5)	14.66 (6.4)	139	60.5	89.3	12-35	"Significant clearance of tumour but residual tissue"	Radiotherapy and somatostatin analogue
9	242	19	−92	139.91 (52.5)	11.11 (2.9)	116	N/A	37.1 (12 mo post-op)	12-35	"Large volume of residual tissue"	Radiotherapy and somatostatin analogue
10	21.6	4.5	−80	35.19 (15.6)	4.86 (21.6)	56.3	74.9	70.2	7-30	"Significant residual tissue"	Radiotherapy and somatostatin analogue

IGF-1; insulin-like growth factor-1.

TABLE 4 Stratified predictive value of postoperative 0800 GH (growth hormone) on nadir OGTT (oral glucose tolerance test) GH, 5 and 13-point GH profiles

Fasting 0800 GH (μg/L)	OGTT Nadir <1.0 μg/L	OGTT Nadir <2.5 μg/L	OGTT Nadir >2.5 μg/L	5-point mean <1.0 μg/L	5-point mean <2.5 μg/L	5-point mean >2.5 μg/L	13-point mean <1.0 μg/L	13-point mean <2.5 μg/L	13-point mean >2.5 μg/L
<1.0	8/9 88.9%	9/9 100%	0/9 0%	8/11 72.7%	11/11 100%	0/11 0%	7/11 63.6%	11/11 100%	0/11 0%
<2.5	11/13 84.6%	13/13 100%	0/13 0%	10/16 62.5%	16/16 100%	0/16 0%	9/16 56.3%	16/16 100%	0/16 0%
2.5-5.0	1/3 33.3%	2/3 66.6%	1/3 33.3%	1/3 33.3%	1/3 33.3%	2/3 66.6%	1/3 33.3%	1/3 33.3%	2/3 66.6%
>5.0	0/3 0%	0/3 0%	3/3 100%	0/5 0%	0/5 0%	5/5 100%	0/5 0%	0/5 0%	5/5 100%

Concern remains with regard to IGF-1 assay standardization.[27] One study group studied all 23 centres participating in the UK National External Quality Assessment Service (NEQAS) for IGF-1 with a clinical scenario.[23] Each centre was asked to measure IGF-1, interpret the result and provide the source of their reference ranges. A 50% variation was found in the upper limit of the reference ranges between centres using the same method. Overall, 30% of the IGF-1 results were against the diagnosis.[23] Other authors involved in The Society for Endocrinology Acromegaly database have proposed the centralizing of IGF-1 and comparison with local results to enhance the quality of UK data. Against this background, the option of a GH profile may be attractive to some sites uncertain of or concerned by their IGF-1 assay performance.

The relationship between serum GH levels above 20 μg/L and IGF-1 plateaus.[4-7] This effect has led to some concern that postoperative IGF-1 levels in large and metabolically active tumours may not adequately reflect partial therapeutic success. Five patients in our cohort had 0800 GH (≥20 μg/L) preoperatively. Reductions in GH postoperatively appeared promising; however, serum IGF-1 remained elevated and all of these 5 patients required additional therapies postoperatively. Three of the 5 received external pituitary irradiation treatment in fractionated doses, and all received somatostatin analogue therapy. Persistent disease in this group was reflected in a persistently elevated IGF-1 at 6 months postoperatively. The use of a 13-point GH profile in these patients did not influence their overall management.

The Acromegaly Consensus Group proposed biochemical criteria for cure of acromegaly in 2010.[24] They recommended cut-off values <1.0 and <0.4 μg/L for random GH and nadir GH on OGTT, respectively, as reflecting disease control when combined with a normal IGF-1. The 2014 Endocrine Society guidelines opt for a serum GH of 0.14 μg/L as indicating "surgical remission" and a level of <1.0 μg/L as indicative of "control" with a normalized mortality risk. At the 3-6 months postoperative reassessment point, discordance between GH measures and IGF-1 may present a management dilemma.[25] Close follow-up with serial measurements over the following year is advocated.[20,29] The slower decline in IGF-1 compared to GH seen after surgery may be explained by differences in the half-life between the 2 hormones and their binding proteins. The variation in IGF-1 with age, gender, body mass and concomitant disease states adds to the potential for discrepancy. Patients in this cohort with IGF-1 > 100 nmol/L had repeat sampling at 6-12 months which often demonstrated a further reduction without additional treatment.

The use of 5-point GH day curves has been advocated over random GH measures as it accommodates some degree of GH pulsatility in GH secretion. Day curves have also been suggested as a means for discriminating those patients with discordant GH and IGF-1 measurements postoperatively.[8,9] More recent evidence however suggests that it is the basal GH secretion rather than peak/pulsatile secretion that determines the serum IGF-1.[28] In keeping with this, a recent meta-analysis of discordant IGF-1/GH studies in treated acromegaly demonstrated that using mean GH profiles produced the highest rates of discordance with IGF-1 compared to random GH and OGTT nadir GH.

For those patients in whom remission is not achieved and disease control is the aim, a number of authors have advocated GH levels of <2.5 μg/L as being associated with a normalization of the mortality risk and thus a therapeutic target.[25,26,30,31] Where this is the case, it has been demonstrated that a single 0800 GH sample of <2.5 μg/L is strongly predictive of a similar result when assessed by OGTT or GH day curve. A similar relationship was reported for 0800 GH >5.0 μg/L whilst those in the range 2.5-5.0 μg/L warranted dynamic testing.[32] These patterns were also demonstrated in our cohort albeit with very small numbers.

Overall, there remains considerable challenge in the biochemical assessment of acromegaly following treatment where there is discordance between GH and IGF-1. In many cases, serial retesting over the following months will clarify disease control or relapse. Ambiguity persists with regard to the appropriate cut-offs for GH and similarly so for adjustment of IGF-1 for confounding variables. There is a need for further research into the natural history of patients with discordant biochemistry following treatment for acromegaly. Our discordant cases here are too few to draw any meaningful conclusions.

5 | CONCLUSIONS

Growth hormone profiling is not necessary for assessing the majority of patients with acromegaly if there is confidence in the local insulin-like growth factor-1 assay. When undertaken, a 5-point profile is adequate rather than a 13-point profile which would require an inpatient stay and does not appear to add value to the overall assessment.

ACKNOWLEDGEMENTS

Mrs Margaret McDonnell, Endocrine Laboratory, Royal Victoria Hospital, Belfast.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

AUTHOR CONTRIBUTIONS

Robert D'Arcy and Karen Mullan have contributed to collating clinical cases, statistical analysis and writing the manuscript. Hamish Courtney, Una Graham, Steven Hunter and David McCance have contributed to case provision and to editing the manuscript.

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How to cite this article: D'Arcy R, Courtney CH, Graham U, Hunter S, McCance DR, Mullan K. Twenty-four-hour growth hormone profiling in the assessment of acromegaly. *Endocrinol Diab Metab*. 2018;1:e7. https://doi.org/10.1002/edm2.7